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Desmopressin Reverses Overly Rapid Serum Sodium Correction in a Hyponatremic Patient Undergoing Living Donor Liver Transplantation: A Case Report

Short Title: Desmopressin slows sodium rise in liver transplant

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Abstract

Patients with end-stage liver disease are often hyponatremic due to multiple physiologic processes associated with hepatic failure. For severely hyponatremic patients undergoing liver transplantation, intraoperative ~~sodium~~ management of serum sodium concentration ($[Na]_s$) is challenging. ~~Serum sodium concentration~~ $[Na]_s$ tends to increase during transplantation by the administration of fluids with higher sodium concentration than the patient's $[Na]_s$. An overly rapid ~~sodium correction~~ increase in $[Na]_s$ (> 1 mEq L^{-1} h^{-1}) is difficult to avoid and increases the risk of serious perioperative complications. ~~encephalopathy, prolonged endotracheal intubation and osmotic demyelination syndrome.~~ We report the successful use of intravenous desmopressin to reverse an overly rapid~~ly~~ ~~rising~~ rise in $[Na]_s$ during living donor liver transplantation.

Introduction

Chronic hyponatremia is common in patients with end-stage liver disease (ESLD). Management of hyponatremia around the time of liver transplantation is challenging because of the pathophysiology of ESLD and fluid shifts during surgery. Low serum sodium concentration ($[Na]_S$) inevitably increases during transplantation, and overly rapid correction is associated with longer postoperative endotracheal intubation, hospital length of stay, and neurologic complications including osmotic demyelination syndrome ~~(ODS).~~[1-4] This report describes the successful intraoperative use of desmopressin as rescue therapy to reverse ~~the~~ an overly rapid rise in $[Na]_S$ ~~correction of hyponatremia~~ in a preoperatively hyponatremic patient undergoing living donor liver transplantation (LDLT).

Written HIPAA authorization was obtained from the patient for publication of this case report. This report discusses the off-label use of desmopressin acetate for re-lowering the $[Na]_S$ of a hyponatremic patient. Desmopressin is approved by the U.S. Food and Drug Administration for treatment of hemophilia A, von Willebrand's disease (Type I), central diabetes insipidus, and nocturnal polyuria.

Case Description

A 57-year-old, 79 kg female with decompensated cirrhosis and hepatocellular carcinoma secondary to hepatitis C was scheduled for LDLT. Her cirrhosis was complicated by chronic hyponatremia, volume overload, hepatic encephalopathy, and thrombocytopenia. The patient was taking furosemide and spironolactone for ascites management, and these medications likely contributed to her hyponatremia. The $[Na]_s$ had fluctuated between 125-130 mEq/L for six weeks prior to transplantation, eventually reaching 124 mEq/L the day of surgery. The preoperative laboratory results included serum creatinine concentration 1.26 mg/dL, total bilirubin 3.8 mg/dL, international normalized ratio (INR) 1.8, hemoglobin 10.5 g/dL, and platelet count 46 x 10^9/L. The Model for End-Stage Liver Disease (MELD)-Na score was 28, which is associated with a three-month mortality of about 20%.

The patient was brought to the operating room for right lobe LDLT. Several measures were implemented early in the operative course to limit the rate of increase in $[Na]_s$ (Figure). A hypotonic crystalloid infusion was administered throughout the operation. Half-normal (0.45%) saline was selected over 5% dextrose because of a history of diabetes. The serum glucose concentration ranged from 88-181 mg/dL and was maintained with an IV insulin infusion. Volume loss from drainage of ascites was replaced with 25 g of 25% albumin, rather than 5% albumin, to minimize sodium administration. Intravenous furosemide and chlorothiazide were administered to promote natriuresis. Autologous cell salvage and transfusion of packed red blood cells

(RBCs) were performed with a Continuous AutoTransfusion System (C.A.T.S.®, Fresenius Kabi, Bad Homburg, Germany) using the high-quality wash setting, which brings the [Na] of the RBC supernatant to approximately that of normal saline (Table 1). No sodium bicarbonate was administered. Despite these measures, $[Na]_s$ increased rapidly following transfusion of fresh frozen plasma (FFP) and platelets (Figure) required to treat coagulopathy and severe thrombocytopenia (nadir fibrinogen concentration 102 mg/dL, peak INR 2.2, and intraoperative nadir platelet count 21 x 10^9/L). $[Na]_s$ increased to 132 mEq/L by the sixth hour of surgery, representing a rate of change greater than 1 mEq L^{-1} h^{-1}.

Considering the $[Na]_s$ trajectory and the need for ongoing transfusions, we administered desmopressin 24 µg (0.3 µg/kg) IV over 20 minutes in an attempt to reverse the rapid increase in $[Na]_s$. Subsequently, $[Na]_s$ decreased linearly over the next four hours to 128 mEq/L (Figure). The overall increase in $[Na]_s$ was less than 0.5 mEq L^{-1} h^{-1} for the remainder of the perioperative period despite ongoing FFP and platelet transfusions.

The surgery lasted 7.3 hours. Fluid balance consisted of administration of 2.7 L crystalloid solution, 6 units packed RBCs, 12 units FFP, and 8 units of platelets obtained by apheresis, 3 L urine output, and 2.5 L estimated blood loss. The endotracheal tube was removed on postoperative day one. $[Na]_s$ remained between 130-134 mEq/L for the first four days after surgery and plateaued at 136 mEq/L at hospital discharge on postoperative day nine. The patient recovered without neurologic complication.

Discussion

Severe hyponatremia ($[Na]_S$ < 125 mEq/L) has a prevalence of 5.7% among cirrhotic patients.[5] Hyponatremia is caused by the release of physiologic mediators in response to systemic vasodilation during ESLD. Vasodilation activates the renin-angiotensin-aldosterone system, the sympathetic nervous system, and release of antidiuretic hormone from the posterior pituitary. These changes act to restore circulating blood volume and perfusion pressure through systemic vasoconstriction, sodium reabsorption, and decreased free water excretion.[6,7] This impaired capacity to excrete urinary free water leads to a dilutional hypervolemic hyponatremia.

Hyponatremia in ESLD is associated with severe ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, encephalopathy, and overall worse outcomes.[5] During chronic hyponatremia brain cells adapt to lower plasma osmolarity by reducing the amount of solute in their cytoplasm. This adaptation decreases the osmotic pressure gradient and minimizes cellular swelling and cerebral edema.[1,8] With rapid correction of hyponatremia, normalization of serum osmolarity may outpace the cell's ability to recapture the lost osmolytes[8] and lead to astrocyte cell death, breakdown of the myelin sheath, disruption of the blood-brain barrier,[9] and possibly ODS. Patients with advanced liver disease are at high risk for ODS[8] which imparts a grim prognosis.[2] The overall incidence of ODS in liver transplantation is reported as 0.5%-1%,[2] but the risk is higher in patients with preoperative hyponatremia, higher MELD-Na scores, and greater swings in perioperative $[Na]_S$.[10]

For hospitalized liver failure patients with asymptomatic hyponatremia, the recommended serum sodium correction rate is 4-6 mEq/L in 24 hours and should not exceed 8 mEq/L in 24 hours.[8] In reality, it is very difficult to avoid such rates during liver transplantation, particularly in patients with severe hyponatremia. Liver transplant surgery requires considerable intravascular volume repletion, and almost all intravenous fluids and blood products contain relevant amounts of sodium (Table 1).[11] Furthermore, allograft function helps restore sodium homeostasis, thereby promoting rapid $[Na]_S$ correction. If transplantation is anticipated in hours to days, slow preoperative correction of severe hyponatremia can be attempted through fluid restriction and diuretic withdrawal.[7] However, this technique may lead to uncomfortable thirst or worsening ascites for the patient and careful monitoring is required. Preoperative correction was not an option for our patient who was admitted from home just prior to transplantation.

A combined strategy of limiting isotonic intravenous fluids, avoiding sodium bicarbonate, administering hypotonic crystalloid solution, and administering loop diuretics has been proposed to slow the intraoperative increase in $[Na]_S$ during liver transplantation.[12] We recommend implementing some or all of these interventions in patients with severe hyponatremia (Table 2), and frequent intraoperative $[Na]_S$ measurements (at least once per hour). Prothrombin complex concentrate and fibrinogen concentrate were not administered in our case, but may help reduce the sodium load when substituted for large volumes of FFP. However, if all of these strategies fail, another treatment to reverse a rapid intraoperative increase in $[Na]_S$ is required.

Desmopressin is a synthetic vasopressin analogue that activates V_2 receptors in the renal collecting tubules.[13] It may slow or reverse a rapid increase in $[Na]_s$ by increasing free water reabsorption. Desmopressin is an effective and well-tolerated treatment for overcorrection of $[Na]_s$ in hypovolemic hyponatremic patients who may develop a water diuresis after intravascular volume repletion with saline.[8] Restoration of hyponatremia by desmopressin appears to be safe and may improve acute neurologic symptoms concerning for impending osmotic demyelination syndrome ~~ODS~~.[14]

To our knowledge, the intraoperative use of desmopressin to reverse an overly rapid rise in $[Na]_s$ ~~correction of hyponatremia~~ in a preoperatively hyponatremic patient has not ~~to our knowledge,~~ previously been ~~described in the literature~~ reported. In our case, desmopressin helped to counteract the rapid increase in $[Na]_s$ ~~from~~ caused by administration of large volumes of sodium-rich FFP and platelets during liver transplantation (Figure). The optimal dose and timing of administration of desmopressin for this purpose has not been established. ~~Previous work has recommended~~ Doses of 2-4 µg IV every 8 hours have been recommended for the treatment of hypovolemic hyponatremic patients ~~with~~ for $[Na]_s$ correction > 1 mEq L^{-1} h^{-1}.[7,14] However, a robust antidiuretic effect is seen with the higher dose of 0.3 µg/kg when administered for platelet dysfunction or active bleeding. This dosage is well-tolerated by adult patients.[13] Since we were facing ongoing coagulopathy and thrombocytopenia in addition to $[Na]_s$ overcorrection, the higher dose of desmopressin was administered in the hope of dual benefit. Following this single dose, $[Na]_s$ decreased to a safe level despite ongoing FFP and platelet transfusions.

Desmopressin is generally safe, but can reduce $[Na]_S$ to a greater degree than desired, which in severe cases can lead to cerebral edema, seizures, and death.[15] Pediatric patients may be at increased risk.[15] ~~After a dose of~~ Following desmopressin administration, ~~frequent~~ $[Na]_S$ ~~measurements~~ must be ~~performed~~ frequently monitored ~~and trended into the postoperative period in order~~ to ~~identify~~ avoid over- or undercorrection.

In conclusion, intraoperative management of chronically ~~hyponatremia in~~ hyponatremic patients undergoing liver transplantation is ~~a~~ common and challenging. ~~problem.~~ $[Na]_S$ often rises at dangerous rates and no established treatment protocol currently exists. Although further studies are necessary, our experience suggests that desmopressin may be a safe and effective intervention to reverse a rapid increase in $[Na]_S$ during liver transplantation, thereby possibly reducing the risk of associated postoperative complications including osmotic demyelination syndrome. ~~ODS.~~ We recommend that desmopressin be considered during liver transplantation when the absolute increase in $[Na]_S$ exceeds 8 mEq/L or there is a sustained increase exceeding 1 mEq L^{-1} h^{-1}, especially when additional transfusions are expected and other interventions have failed (Table 2).

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Table

Table 1. Sodium content of intravenous fluids commonly administered during liver transplantation.

Type of Fluid		Sodium Content (mEq/L)
Crystalloids	Dextrose 5% water	0
	0.45% (half-normal) saline	77
	0.9% (normal) saline	154
	Lactated Ringer's	130
	Plasma-Lyte	140
Colloids	5% albumin	130-160
	25% albumin	130-160
Blood products	Platelets	172
	Fresh frozen plasma	170

Table 2: Interventions to limit the increase in serum sodium concentration in patients with severe chronic hyponatremia during liver transplantation.

Minimize sodium administration
Administer hypotonic crystalloid infusion (dextrose 5% water or 0.45% saline)
Avoid sodium bicarbonate (8.4% solution has a sodium content of 1000 mEq/L)
Substitute prothrombin complex concentrate and fibrinogen concentrate for FFP
Maximize sodium excretion
Administer loop and thiazide diuretics
Increase free water reabsorption
Administer desmopressin

FFP; fresh frozen plasma.

Figure Legend:

Figure. Blue line and filled circles: perioperative course of serum sodium concentration ($[Na]_s$). Shaded gray area: operating room time. Dashed lines: modeled trajectory of increase in $[Na]_s$ of 1 mEq L^{-1} h^{-1} (*red line*) and 0.5 mEq L^{-1} h^{-1} (*black line*) from case start. Yellow and green circles: times of transfusion of fresh frozen plasma (FFP) and platelets. Cyan and magenta diamonds: times of administration of 500 mL of half-normal saline (1/2NS) and 50 mL of 25% albumin (Alb). Blue arrow: time of desmopressin administration. X: time of tracheal extubation.